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# A Randomized Controlled Trial to Assess the Impact of Clinical Pharmacy Interventions on Treatment Outcomes, Health Related Quality of Life and Medication Adherence Among Hepatitis C Patients

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**Purpose:** The role of specialized pharmacy services remains unexplored in clinical practice for hepatitis C patients in Pakistan. This study aimed to evaluate the impact of clinical pharmacy interventions on treatment outcomes, health-related quality of life (HRQoL), and medication adherence among hepatitis C patients.

**Methods:** A randomized control trial was conducted at two tertiary-care teaching hospitals in Pakistan. Hepatitis C patients who attended the outpatient clinics between October 2015 and September 2018 were randomized to two groups [usual care (UC) and pharmaceutical care (PC)] in a 1:1 ratio, applying simple envelope method. The PC group received pharmaceutical care led by a clinical pharmacist. The care that patients received included education and counseling on medication compliance, labeling of medication packs, and monitoring of adverse drug events, led by a qualified clinical pharmacist during the 15- to 20-minute monthly sessions, while the UC group received standard care at hospital, which did not involve clinical pharmacist input. Outcome measures, such as sustained virological response, HRQoL, and adherence rate (pharmacy data) were assessed at enrolment and distinct time intervals: 4 weeks, 8 weeks, and end of treatment.

**Results:** A total of 931 patients were included in the study (UC 466 and PC 465), with mean age 42.35±1.9 years. Sustained virological response at 12 weeks was achieved in 86.0% patients in the PC group, significantly ( $p<0.001$ ) higher than the UC (69.3%) group. Fewer patients (9.9%) in the PC group reported mobility problems, significantly fewer ( $p<0.001$ ) than the UC group (11.8%). Self-care, usual activity, pain, and depression were relieved significantly in the PC group compared to the UC group. The EuroQol visual analogue scale (baseline 56.1 of UC group versus 55.2 for PC group) was raised to 71.8 and 71.9 in the UC and PC groups, respectively. Medication adherence was significantly improved ( $p<0.001$ ) in the PC group (88.6%) when compared to the UC group (77.9%, 95% CI 88.9%–91.9%).

**Conclusion:** Pharmacist-led clinical pharmacy interventions as part of multidisciplinary care had a significant impact on improving cure rates, HRQoL, and medication adherence for hepatitis C patients. This study suggests that clinical pharmacists should be incorporated into the multidisciplinary health-care team for care of hepatitis C patients.

**Keywords:** hepatitis C, clinical pharmacy, medication adherence, clinical outcomes, quality of life

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## Introduction

Hepatitis C virus (HCV) infection is a health-care problem worldwide.<sup>1</sup> The estimated global prevalence of HCV has been reported to be approximately 2.2%–3.0%

(130–170 million people) in the literature.<sup>1–3</sup> Recent advances in HCV pharmacotherapies and the development of a World Health Organisation HCV-elimination strategy has resulted in a significant increase in “test and treat” programs.<sup>4–6</sup> Novel direct acting antiviral (DAA)–based therapies are effective in 95% of HCV patients.<sup>7</sup> However, long-term therapy with DAAs and pill burden often results in nonadherence that leads to suboptimal treatment outcomes in HCV patients.<sup>8–10</sup>

Although the major determinants of therapeutic response to pharmacotherapy include HCV genotype and viral load, additional factors, such as medication adherence and optimal duration of treatment, contribute to therapeutic outcomes.<sup>11</sup> Various studies have highlighted the significance of educating patients to improve adherence and treatment outcomes, including education on treatment schedules and side effects, especially prior to initiation of antiviral therapy.<sup>12–14</sup>

The key element of effective HCV clinical management is access to a multidisciplinary team (MDT).<sup>15</sup> As a member of a multidisciplinary team, the pharmacist is in an ideal position to serve patients with chronic HCV, not only through patient counseling regarding the disease state, therapeutic regimen, and associated adverse events but also by educating patients on the vital role of treatment adherence in the achievement of optimal therapeutic outcomes.<sup>16</sup> Pharmacist interventions and patient education on medication use have played a central role in improving adherence and management of other chronic diseases.<sup>17,18</sup> The European Society for the Study of the Liver in 2018 also emphasized the<sup>19,20</sup> vital role of pharmacists in educating patients on potential drug–drug interactions (DDIs) and improving adherence to the treatment regimen that will eventually result in significant improvement in health-related quality of life (HRQoL) for all patients receiving HCV therapies.<sup>21</sup>

A recent comprehensive pharmaceutical care programme in Spain demonstrated improved adherence and treatment outcomes in HCV patients.<sup>22</sup> A similar pilot study revealed that safe and effective management of HCV infection can be achieved through the involvement of clinical pharmacists in patient care.<sup>23</sup> Published studies have unveiled significant improvement in treatment outcomes as a consequence of clinical pharmacist–led and person-centered care.<sup>24–26</sup> Limited literature exists on the role of pharmacists in optimization of treatment regimens and management of adverse effects in HCV infection,<sup>27</sup> particularly in the context of low- and middle-income countries (LMICs). LMICs harbour 80% of the global HCV burden. Currently, Pakistan has

approximately 10 million HCV patients, and health-care system is not fully equipped with clinical pharmacists specialized in chronic HCV.<sup>28</sup> Alongside this considerable burden, there is limited literature on the context of benefits of pharmacist interventions within the infrastructure of health care in LMICs among HCV patients being treated with new DAAs. This study aimed to evaluate the impact of pharmacist-led clinical interventions on treatment outcomes, HRQoL, and medication adherence in HCV patients in Pakistan.

## Methods

### Study Design

A randomized control study was undertaken. The allocation ratio was 1:1.

### Participants and Eligibility

Confirmed HCV-positive patients aged  $\geq 18$  years who presented to the gastroenterology department or HCV clinic during the study period were eligible for inclusion in the study. Those had been initiated on DAA treatment [sofosbuvir (Sof), daclatasvir (Dac), or a combination thereof with or without ribavirin (Rv)] and had given informed consent were enrolled in the study. All patients who were pregnant or coinfecting with HBV, HDV, or autoimmune hepatitis were excluded.

Patients were recruited from the outpatient clinic of gastroenterology departments at two tertiary-care hospitals in Islamabad and Lahore with a combined bed capacity of 2,346 (1,150 and 1,196 respectively). These hospitals have dedicated pharmacies to dispense HCV medicines to referred patients. The hospitals included in the study accept referrals from primary- and secondary-care hospitals, as well as basic health-care units situated in remote areas of Pakistan. This study was conducted between October 2015 and September 2018. Patients were divided into two groups [usual care (UC) and pharmaceutical care (PC)]. Written consent was obtained from each recruited patient, and all patients had the purpose and conduct of the study explained to them. Any queries raised by patients were addressed to satisfy each recruited subject.

### Usual Care (Control)

This group was given usual care by the hospital staff, which included the input of physicians, a nurse, and/or pharmacy technician. They were treated in accordance with the routine clinical practices of hospital, which include diagnosis, dispensing/issuance of medication by hospital-pharmacy staff,

and routine follow-up of patients at the health-care facility. They did not receive interventions from the pharmacist. These patients were provided guidance as per their requirements, and were not bound to attend any pharmacists' counseling session. Hospital staff were also informed to refer their patients to a pharmacist for any additional medicine-related information or guidance.

## Pharmaceutical Care (Interventional)

In addition to usual care, all the patients in the PC group were provided with individualized patient care provided by a clinical pharmacist. The additional care provided by the pharmacist included direct patient monitoring, education on lifestyle modifications, and counseling on the appropriate use of HCV medication. All patients who consented to the pharmacist's counseling session were enrolled at baseline and followed up until 12 weeks after the end of treatment. Each patient was instructed to report to the pharmacist every month during his/her visit for routine checkup by the physician. Clinical pharmacy services continued until treatment completion. Moreover, patients were asked to inquire any information pertaining to the medication by telephone after the end of treatment.

## Patients' Pharmaceutical Care and Interventions

Individualized patient care comprised the following:

1. Pharmacist counseling (15- to 20-minute sessions) on the proper use of medication and the provision of an educational pack inclusive of medication diary, a laboratory profile book, and a medication-adherence chart.
2. Labeling of medication packs to assist pill sorting. Labels included instructions on dose and frequency/timing of medication doses.
3. Patient education using both oral and written approaches. This protocol included an educational leaflet pertaining to medicine administration, medicine storage, and lifestyle modification.
4. Detection or assessment of potential DDIs by a pharmacist prior to start of treatment and recommendations for their management.
5. Pharmacist counseling on the safe use of medication (self-medication or over-the-counter [OTC] medicines), monitoring, and prompt detection of adverse drug events (ADEs).

A trained pharmacist provided the interventions described at each health-care facility, along with the existing pharmacy staff during the study period. The educational materials were delivered in Urdu (local language). The pharmacist was responsible for monitoring adherence to the HCV treatment. Patients were interviewed at their first visit and follow-up visit each month in a dedicated room adjacent to the gastroenterologist's office. Information pertaining to medicine usage, missed doses/adherence, hematology and biochemistry data, incidence of any ADE, and evaluation of clinical outcomes was retrieved from patients. Medication usage and missed doses were monitored by retrieving the empty blister packs of medicines from the patients in the pharmacy area, followed by a pill count.<sup>27</sup> Additionally, dose charts (filled) were retrieved from the patients. Any missing information was requested verbally from the patient. A separate room was availed for patients' counseling sessions and interviews and to avoid any contamination with the UC group. The clinical pharmacist had no access to or was not involved in the care of the patients in the UC arm. To maintain the ethical role of health-care provision, at the end of the study all patients who attended the gastroenterology clinic after screening were provided with an educational booklet containing information on preventive care for family members.

## Outcome Measures

The primary outcome measure was sustained virological response at week 12 posttreatment (SVR12),<sup>29,30</sup> while secondary outcome measures were assessment of number of ADEs, HRQoL, and medication adherence.

## Sustained Virological Response

Clinical outcomes were assessed based on HCV viral load measured at baseline, end of treatment, and 12 weeks after the end of treatment (SVR12). A viral load of <12 IU/mL at 12 weeks after the end of treatment was considered undetectable and regarded as "cure".<sup>31</sup> HCV RNA levels were measured using an Abbott m2000 real-time HCV assay. Samples were sent to allied laboratories of these hospitals for reporting of quantitative viral loads through PCR. Data were extracted from the medical records of patients for this parameter.

## Adverse Drug Events, DDIs, and Concomitant Medicines

The incidence of ADEs was assessed by trained pharmacist based on the Common Terminology Criteria for Adverse

Events version 4.<sup>32</sup> Data pertaining to ADEs were collected at three time intervals: 4 weeks, 8 weeks, and 12 weeks from the start of treatment in both arms. Assessment of clinical potential DDIs, as well as recommendations for DDI management, were made in accordance with the Drug Interaction Checker, University of Liverpool (<http://www.hep-druginteractions.org>). The number and type of concomitant medications used was assessed based on the previously published literature<sup>19</sup> and 73<sup>rd</sup> edition of the *British National Formulary*.

## Health-Related Quality of Life

HRQoL was assessed at three time points: before, during, and after treatment (at day 1, 8<sup>th</sup> week, and 12<sup>th</sup> week (end of treatment)). A validated tool (EuroQol 5D-3L) was administered by the researcher during the patient's visit to the pharmacy. The EQ-5D-3L consists of five dimensions: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. These dimensions were dichotomized into two levels for analysis, ie, patient has no/mild problems (level 1) and patient has moderate/severe problems (level 2). The EQ VAS records the patient's self-rated health on a scale numbered from 0 (worst perceived health) to 100 (best perceived health).<sup>33</sup>

## Medication Adherence

Medication adherence was measured using data of pharmacy refills (obtained from the pharmacy database). Pharmacy refills were recorded at patients' hospital visits each month. Data relating to adherence was collected at three time intervals: 4 weeks, 8 weeks, and 12 weeks from the start of treatment. The total number of pharmacy refills attended by each patient divided by the number of advised refills by 100 was the algorithm used to calculate<sup>34,35</sup> Finally, adherence was measured as the proportion of patients who had taken at least 80% of their prescribed doses. The metric was used as an approximation of the 80/80/80 rule. This rule refers to the greater possibility of successful treatment outcome that is associated with taking 80% of doses and 80% of the prescribed treatment duration.<sup>35</sup>

## Sample Size

Based on the prevalence of HCV infection and sample size that has been reported in the literature,<sup>24,36</sup> we estimated a minimum sample size of 384 from each center (95% CI with confidence interval 5%). The target sample size from the two health-care facilities was 922, taking into account a potential 20% dropout rate. SVR12 was the major outcome measure to assess the success of treatment and power analyses.

## Randomization

Enrolled patients were randomized at a ratio of 1:1 using a simple envelope method with modification.<sup>37</sup> Briefly, the physician at the time of first visit/diagnosis picked one of the envelopes marked UC or PC alternately, which was the assigned to patients.<sup>36,37</sup> A separate room was availed for patients' counseling sessions and interviews and to avoid any contamination with the UC group. The pharmacist had no access to or was not involved in the care of patients in the UC arm. The principal investigator (TR) was responsible for checking the pharmacists to assure the delivery of all components of the interventions as intended.

## Data Sources and Collection

Patient demographics and treatment variables were collected on a predesigned data sheet moderated by the research team, which consisted of a senior medical consultant, a specialist pharmacist, and a statistician. Data extraction was carried out by the principal investigator and validated by the gastroenterologist. Variables were age, sex, HCV genotype, HCV viral load, liver-health status, presence of comorbidities, concomitant medication, baseline hematology and biochemistry data, and treatment regimens. During follow-up visits (at weeks 4, 8, and 12), each variable was re-recorded to assess any changes.

The information was obtained from patients' profiles and electronic records available via the hospital database and the logistics management and information system. All data were anonymized by the data collector prior to analysis by the research team. Data sets were stored on a password-protected computer at the Department of Pharmacy, Quaid-i-Azam University, Islamabad, Pakistan. The necessary ethical approvals were obtained from the Ethical Review Board of PIMS Hospital Islamabad (F.1-1/2015/ERB/SZABMU), SIMS (IRB/2017/333/SIMS), and the Bioethics Committee of Quaid-i-Azam University, Islamabad (DFBS/2015-248). All questionnaires or tools were adopted after the necessary permissions from the corresponding organizations or the authors.

## Statistical Analysis

Statistical analyses were performed using SPSS version 24. Frequency distribution and descriptive statistics were calculated for demographics. Results are reported in terms of differences between groups with 95% CIs where appropriate. Pearson's  $\chi^2$  was applied to compare demographic and end-point variables. Mann-Whitney *U* tests were



conducted to compare groups. McNemar's  $\chi^2$  was used to analyze whether changes in percentage HRQoL between the PC group and UC group were significant.<sup>38</sup> Missing data were analyzed by missing-value analysis with SPSS and any missing values replaced by mean values.  $p \leq 0.05$  was taken as statistically significant.

## Results

Overall, 1,050 patients were enrolled. Of those, 931 were eligible for randomization postscreening (n=757 from hospital A and n=174 from hospital B), while 119 were excluded. All patients consented to take part. Patients were assigned to one of the two groups (UC, n=466; PC, n=465). The mean age of patients was  $42.35 \pm 1.9$  years. There were 418 (44.9%) males and 513 (55.1%) females. Of the total cohort, 671 (72.1%) were urban residents. A total of 109 (11.7%) were

cirrhotic, and genotype 3a the most prevalent genotype (96.6%). There was no significant difference between the UC and PC groups ( $p=0.88$ ) for baseline viral load; Table 1 and Figure 1).

[CONSORT diagram (Figure 1) to appear here]

The treatment regimen Sof/Rv was the most prescribed for 608 (65.3%) patients, followed by Sof/Dac/Rv for 201 (21.5%) and Sof/Dac for 13.1%. Baseline characteristics of patients and treatment regimens are summarized in Table 1.

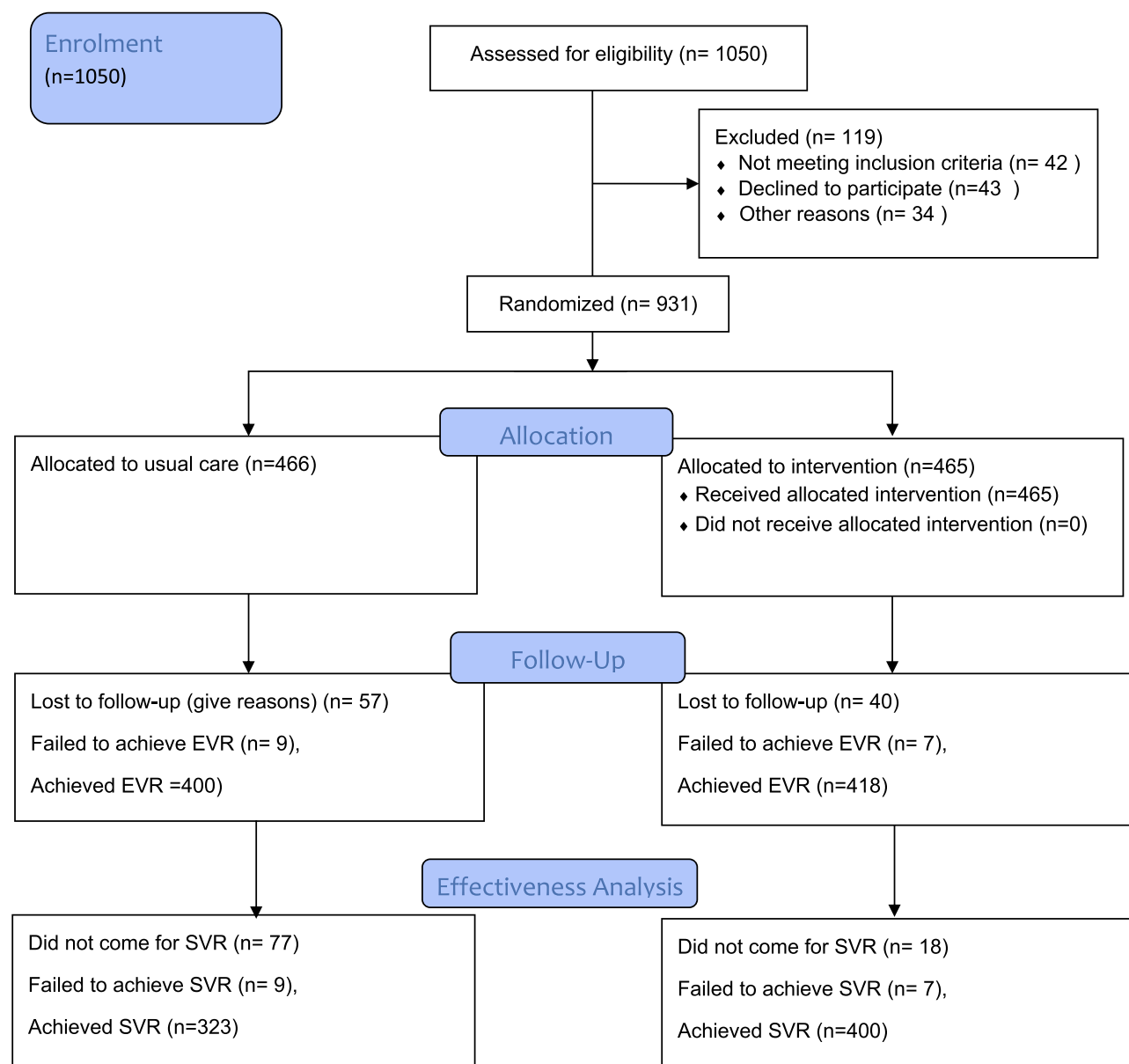
## Clinical Outcomes

A total of 400 (86.0%) patients in the PC group achieved SVR12, significantly ( $p < 0.001$ ) more than the UC group — 323 (69.3%). A total of 192 (20.6%) did not attend their 12-week posttreatment follow-up appointment (134 [28.8%] UC group vs 58 [12.5%] PC group,  $p < 0.001$ ). Overall, 287

**Table 1** Baseline Demographic and Clinical Characteristics of Study Population

		All Patients (n=931)	UC Group (n=466)	PC Group (n=465)
Age, years	Mean $\pm$ SD	$42.35 \pm 1.9$	$42.85 \pm 1.7$	$41.84 \pm 1.7$
	<40	439 (47.15%)	213 (45.7%)	226 (48.6%)
	41–60	439 (47.15%)	225 (48.3%)	214 (46.0%)
	>60	53 (5.7%)	28 (6.0%)	25 (5.4%)
Sex	Males	418 (44.9%)	215 (46.1%)	203 (43.7%)
	Females	513 (55.1%)	251 (53.9%)	262 (56.3%)
Residence	Urban	671 (72.1%)	329 (70.6%)	342 (73.6%)
	Rural	260 (27.9%)	137 (29.4%)	123 (26.4%)
Liver-health status	Cirrhotic	109 (11.7%)	47 (10.1%)	62 (13.3%)
	Noncirrhotic	822 (88.3%)	419 (89.9%)	403 (86.7%)
Diagnosis	HCV/CHC	905 (97.2%)	458 (98.3%)	447 (96.1%)
	HCV + comorbidities	26 (2.8%)	8 (1.7%)	18 (3.8%)
Genotype	Untypeable/mixed	8 (0.8%)	2 (0.4%)	6 (1.3%)
	1/1a	9 (1.0%)	4 (0.9%)	5 (1.1%)
	1b	4 (0.4%)	3 (0.6%)	1 (0.2%)
	3a	899 (96.6%)	451 (96.8%)	448 (96.3%)
	3b	11 (1.2%)	6 (1.3%)	5 (1.1%)
Treatment history	Naïve	920 (98.8%)	459 (98.5%)	461 (99.1%)
	Previously treated	11 (1.2%)	7 (1.5%)	4 (0.9%)
Viral load (baseline)	Very low viremia	24 (2.6%)	13 (2.8%)	11 (2.4%)
	Low viremia	22 (2.4%)	13 (2.8%)	9 (1.9%)
	Moderate	287 (30.8%)	139 (29.8%)	148 (31.8%)
	High viremia	275 (29.5%)	139 (29.8%)	136 (29.2%)
	Positive	323 (34.7%)	162 (34.8%)	161 (34.6%)
Treatment choices	Sof/Rv	608 (65.3%)	307 (65.9%)	301 (64.7%)
	Sof/Dac/Rv	201 (21.5%)	98 (21.0%)	103 (22.2%)
	Sof/Dac	122 (13.1%)	61 (13.1%)	61 (13.1%)

**Abbreviations:** HCV, hepatitis C virus; CHC, chronic hepatitis C; Sof, sofosbuvir; Rv, ribavirin; Dac, daclatasvir; UC, usual care; PC, pharmaceutical care.



**Figure 1** Flow diagram showing patient recruitment and follow-up.

**Abbreviation:** EVR, end-of-treatment virological response; SVR, sustained virological response.

(30.8%) patients presented with a moderate baseline viral load. At the end of treatment, 818 (87.9%) had achieved a response showing viral load below the detectable level, while 16 (1.7%) had failed to achieve a response ( $p=0.16$ ). Viral clearance was achieved in 723 (77.7%) patients at 12 weeks after the end of treatment, ie, SVR12, while 16 (1.7%) failed to achieve SVR12. Table 2 contains the clinical outcomes of both groups included in the study.

## Adverse Drug Events

Fewer patients (38 [8.2%]) experienced an ADE in the PC group than the UC group (49 [10.5%]). Dyspepsia/

gastroesophageal reflux was the most frequent ADE ( $n=20$  [3.8%] in UC and  $n=14$  [2.9%] in PC), followed by anemia ( $n=12$  [2.5%] in UC and  $n=11$  [2.4%] in PC) and fatigue (1.5% and 1.3% in UC and PC groups, respectively; Figure 2)

## Concomitant Medication and Drug-Drug Interactions with DAAs

There were 52 (11.2%) patients in UC group and 47 (10.1%) in the PC group using OTC or regular medications along with the DAAs. When assessed by the pharmacist, the possibility of DDIs between DAAs and self-medicated OTC

**Table 2** Comparison of Outcome Parameters (Adherence and Clinical Outcomes) Among Groups

Outcomes	Subcategories	All Patients (n=931) n(%)	UC Group (n=466) n(%)	PC Group (n=465) n(%)	p-value (UC vs PC)
ETR	ETR (NA) Failed at ETR ETR achieved	97 (10.4%) 16 (1.7%) 818 (87.9%)	57 (12.2%) 9 (1.9%) 400 (85.8%)	40 (8.6%) 7 (1.5%) 418 (89.9%)	0.163
SVR12	Did not have SVR Failed SVR achieved	192 (20.6%) 16 (1.7%) 723 (77.7%)	134 (28.8%) 9 (1.9%) 323 (69.3%)	58 (12.5%) 7 (1.5%) 400 (86.0%)	0
Adherence (pharmacy refills)	≤60% 61%–79% ≥80%	115 (12.4%) 41 (4.4%) 775 (83.2%)	68 (14.6%) 35 (7.5%) 363 (77.9%)	17 (3.7%) 36 (7.7%) 412 (88.6%)	0 0

**Notes:**  $p < 0.05$  considered significant.

**Abbreviations:** HCV, hepatitis C virus; CHC, chronic hepatitis C; ETR, end-of-treatment response; NA, not available; SVR12, sustained virological response at 12 weeks after end of treatment; UC, usual care; PC, pharmaceutical care.

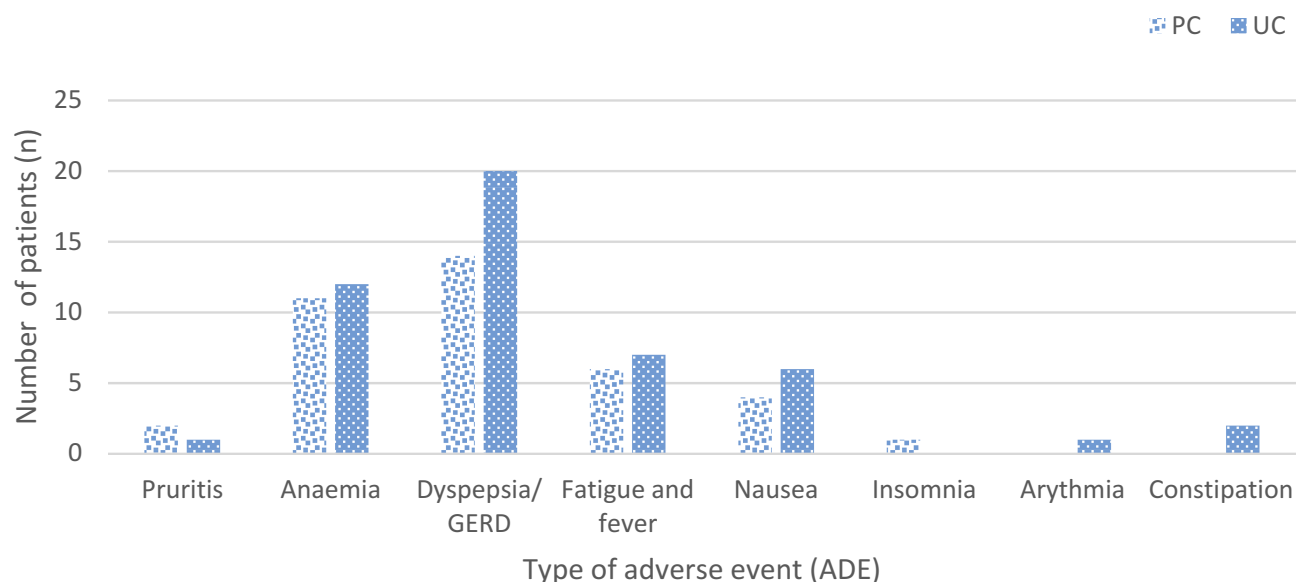
products was low:  $n=8$  (1.7%) in the UC group and  $n=5$  (1.1%) in the PC group. In the UC group, proton-pump inhibitors were the most frequent concomitant medications ( $n=14$ ), followed by multivitamins ( $n=10$ ) and NSAIDs ( $n=6$ ), while in the PC group multivitamins ( $n=12$ ) were the most frequent concomitant medicines, followed by proton-pump inhibitors ( $n=11$ ) and NSAIDs ( $n=8$ ). Table 3 details the potential DDIs identified in the study.

## Health-Related Quality of Life

Before treatment in the UC group, 51.5%, 24.2%, and 15.5% patients reported problems in these dimensions, respectively.

These problems were alleviated significantly ( $p < 0.001$ ) to 11.8%, 4.9%, and 5.8%, respectively, at the end of treatment. In the PC group, baseline dimensions (52.9%, 27.3%, and 15.9%) were relieved significantly ( $p < 0.001$ ) to 10.1%, 4.0%, and 4.1% respectively ( $p < 0.001$ , Table 4).

Overall, 47.0% of patients reported moderate levels of pain or discomfort at baseline that were relieved, and only 0.3% had a complaint of pain at the end of treatment. No significant difference ( $p > 0.05$ ) was observed with regard to reduction in pain between the PC group (baseline 221 [47.5%], final two [0.4%]) and the UC group (baseline 217 [46.6%], final three [0.6%]). However, McNemar's  $\chi^2$

**Figure 2** Comparison of adverse drug events observed between groups (UC vs PC).

**Abbreviations:** UC, usual care; PC, pharmaceutical care.



**Table 3** Drug–drug Interactions Between HCV DAAs and Concomitant Drugs

Care Group	Concomitant Medicines (Type)	n (%)	Sof/Rv (DDI, Management)	Sof/Dac/Rv (DDI, Management)	Dac/Rv (DDI, Management)
PC	Aluminum hydroxide (Al)	3 (0.6)	■ Weak DDI, (2 hour gap)	■ Weak DDI, (2 hour gap)	◆
	Laxatives	1 (0.2)	◆	◆	◆
	Antipruritic	4 (0.9)	◆	◆	◆
	Multivitamins	12 (2.6)	◆	◆	◆
	Benzodiazepines	1 (0.2)	◆	◆	◆
	CV	2 (0.4)	◆	● Amiodarone (alternative)	■ Simvastatin (dose reduction)
	Pepzyme	1 (0.2)	◆	◆	◆
	No concomitant meds	418 (89.9)			
	NSAID	8 (1.7)	◆	◆	◆
	PPI	11 (2.4)	◆	◆	◆
	PPI + multivitamin	2 (0.4)	◆	◆	◆
	PPI + gonadotrophins	1 (0.2)	◆	◆	◆
	PPI + NSAID	1 (0.2)	◆	◆	◆
UC	Aluminium hydroxide (Al)	2 (0.4)	■ Weak DDI, (2 hour gap)	■ Weak DDI, (2 hour gap)	◆
	Al + PPI	2 (0.4)	■ Weak DDI, (2 hour gap)	■ Weak DDI, (2 hour gap)	◆
	Laxatives	2 (0.4)	◆	◆	◆
	Antipruritic	1 (0.2)	◆	◆	◆
	Multivitamins	10 (2.2)	◆	◆	◆
	BC+ anti-pruritic	1 (0.2)	◆	◆	◆
	BC+ Probiotics	1 (0.2)	◆	◆	◆
	Probiotics+ NSAID	1 (0.2)	◆	◆	◆
	CV	2 (0.4)	◆	● Potential DDI, amlodipine	● Nitrendipine, atenolol
	Levothyroxine	2 (0.4)	◆	■ Weak DDI (monitor TF)	■ Weak DDI (monitor TF)
	Ranitidine	1 (0.2)	◆	◆	◆
	Hepatoprotectives	1 (0.2)	◆	◆	◆
	No concomitant meds	414 (88.8)			
	NSAID	6 (1.3)	◆	◆	◆
	PPI	14 (3.0)	◆	◆	◆
	PPI + laxatives	1 (0.2)	◆	◆	◆
	PPI + multivitamins	5 (1.1)	◆	◆	◆

**Notes:** Colour legend adopted from EASL 2018 recommendation ).<sup>19</sup> ◆ No clinically significant interaction expected. ■ Potential interaction; may require a dosage adjustment, altered timing of administration or monitoring. ● These drugs should not be coadministered.

**Abbreviations:** PC, pharmaceutical care; UC, usual care; DAA, direct-acting antiviral; HCV, hepatitis C virus; Sof, sofosbuvir; Dac, daclatasvir; Rv, ribavirin, CV; cardiovascular; PPI, proton-pump inhibitor; BC, Bcomplex; TF, thyroid function.

showed significant ( $p=0$ ) change in HRQoL dimensions between the PC group and the UC group. Moreover, anxiety was significantly reduced ( $p=0.00$ ) in the PC group (baseline 329 [70.8%] vs final 109 [23.5%]) in comparison with the UC group (baseline 343 [73.4%] vs final 104 [22.3%]).

## EuroQol Visual Analogue Scale

Overall, mean EQ VAS was  $55.7 \pm 6.9$ . Baseline EQ VAS for the UC ( $56.1 \pm 7.0$ ) and PC ( $55.2 \pm 6.8$ ) groups rose to  $71.8 \pm 8.4$  and  $71.9 \pm 8.7$ , respectively, showing a significant change in both groups ( $p=0$ , Table 4)

**Table 4** Summary of EQ5D-3L Data for Health Related Quality of Life Domains

Dimensions	All Patients (Reporting Problems)		Patients Reporting Problems in UC Level 2 (n=466)			Patients Reporting Problems in PC Level 2 (n=465)			$\chi^2$ (p-value), UC vs PC
	Baseline, n (%)	Final, n (%)	Baseline, n (%)	Final, n (%)	$\chi^2$ (p-value) <sup>^</sup>	Baseline, n(%)	Final, n(%)	$\chi^2$ (p-value) <sup>^</sup>	
Mobility	486 (52.2)	101 (10.8)*	240 (51.5)	55 (11.8)	20.3 (0)*	246 (52.9)	46 (9.9)	4.3 (0.38)	0.88 (0.35)
Self-care	240 (25.8)	67 (7.2)*	113 (24.2)	21 (4.5)	38.5 (0)*	127 (27.3)	24 (5.2)	12.3 (0)*	0.22 (0.64)
Usual activities	146 (15.7)	46 (4.9)*	72 (15.5)	21 (4.5)	0.023 (0.88)	74 (15.9)	25 (5.4)	2.9 (0.09)*	0.38 (0.54)
Pain/discomfort	438 (47.0)	3 (0.3)*	217 (46.6)	3 (0.6)	3.5 (0.06)	221 (47.5)	2 (0.4)	2.4 (0)*	3.00 (0.08)
Anxiety/depression	672 (72.2)	213 (22.9)*	343 (73.4)	104 (22.3)	8.4 (0.004)*	329 (70.8)	109 (23.5)	11.2 (0.001)*	0.17 (0.68)
EQ5D VAS (Mean $\pm$ SD)	55.7 $\pm$ 6.9	71.8 $\pm$ 8.5	56.1 $\pm$ 7.0	71.8 $\pm$ 8.4	0*	55.2 $\pm$ 6.8	71.9 $\pm$ 8.7	0*	0* <sup>a</sup>

**Notes:**  $p < 0.05$  considered significant. <sup>a</sup>t-test, \*significant value. <sup>^</sup>McNemar  $\chi^2$  showed significant change over time. HRQoL was analyzed considering two levels of each domain (dichotomized), ie, patients with problems and patients with no problem, wherein the two levels were used to mark the changes before treatment and after treatment, as published elsewhere.<sup>49</sup>

**Abbreviations:** EQ, EuroQol; UC, usual care; PC, pharmaceutical care.

## Medication Adherence

Based on pharmacy refills, 775 (83.2%) patients had a >80% adherence rate to the prescribed treatment, with 12.4% of patients receiving <60% of their expected refills vs 3.7% (n=17) of patients in the PC group. Adherence was significantly better (>80% [ $p < 0.001$ ]) in the PC group (412 [88.6%]) than the UC group (363 [77.9%], 95% CI 88.9%–91.9; Table 2).

## Discussion

This study evaluated the impact of introducing a clinical pharmacy service to HCV patients in optimizing clinical outcomes, with an aim to improve medication adherence and HRQoL. Viral clearance results revealed that SVR12 was achieved in 86.0% of PC-group patients and 69.3% in the UC group. Unfortunately, as the DNA rate for SVR12 was significantly higher in the UC group than the PC group (28.8% vs 12.5%), it is difficult to conclude the true SVR12 rates of both groups, as a fair number of the UC group vs the PC group (28.8% vs 12.5%) did not appear for SVR12 follow-up. Despite the high published SVR12 rates seen in the literature with novel DAAs,<sup>39</sup> several factors may have contributed to the slightly decreased SVR12 rate seen in this study: the financial burden to the patient from having to pay for laboratory tests and travel costs being possible factors. An earlier study demonstrated the burden of out-of-pocket costs accrued by patients receiving HCV treatment.<sup>40</sup>

Interestingly, more patients (10.5%) in the UC group experienced ADEs than the PC group (8.2%). Dyspepsia/gastroesophageal reflux was the most frequent ADE (3.8%

in UC and 2.9% in PC). This low incidence of ADEs may be attributed to the increased safety of DAAs in comparison to previous regimens.<sup>41</sup> There were 12.1% of follow-up cases for whom interventions were required, including 49 and 38 patients who experienced ADEs in UC and PC, respectively. Of those, 26 had significant comorbidities. Studies have reported that the provision of specialized pharmacy clinical services, including medication-administration counseling and management of ADEs, improves patient outcomes, and in this study<sup>42,43</sup> 36 (3.9%) patients were specifically counseled by the pharmacist to take their concomitant medicines at different times to the HCV medicines. The GRUviC trial also demonstrated that a comprehensive pharmaceutical care programme involving direct patient counseling before initiation of treatment improves patient education and safety consequently.<sup>22</sup>

Our results show that HRQoL of HC patients was significantly improved in the PC group. According to EQ5D scores, the three most frequent dimensions (of moderate severity) were mobility (49.0%), pain/discomfort (46.7%), and anxiety (70.8%). Similarly, HRQoL complaints (fatigue, depression, and neurocognitive deficits)<sup>44</sup> were reported by Foster et al among HCV patients.<sup>44</sup> These results emphasize the vital role a pharmacist has as a member of the multidisciplinary team, in improving the QoL and disease management of patients with chronic HCV infections. The provision of educational and supportive material in the form of counseling, adequate labeling of medication, medication diaries, and other compliance tools serves to facilitate adherence to routine follow-up tests and encourages patients to take their medication as per prescribed doses.

Our study demonstrates that pharmacist-led individualized patient care of HCV patients is an effective approach that improves patient adherence when following DAA regimens. The adherence rate was significantly improved  $>80\%$  ( $p<0.001$ ) in the PC group 412 (88.6%) over the UC group — 363 (77.9%). Studies have shown that nonadherence to combination therapy is common in routine patients,<sup>8</sup> and clinical trial-adherence data suggest that SVR decreases when patients have  $<60\%$  dose-interval adherence.<sup>45</sup> Our results are also consistent with other interventional studies where pharmacist-led interventions significantly improved patient adherence to medication regimes.<sup>25,36</sup>

This study has explored the role of the pharmacist as a member of the health-care team in the management of HCV. Patient data were collected from two major tertiary hospitals with adequate sample size for the planned statistical analyses. Validated and recognised data sources were used for all information on prescription parameters and clinical outcomes. The study is not without its limitations. Firstly, a significant number of patients did not attend their SVR12 follow-up appointment, hence missing the final assessment by the pharmacist. Secondly, HRQoL complaints may have been underreported by patients who received treatment during their follow-up appointments. Thirdly, this study was specific to the population served by the tertiary-care centers, and may not be representative of the entire patient population affected by HCV in Pakistan. Finally, at the time of the study, DAAs were newly approved for use in hospital B, so the recruited subjects from this health-care facility were fewer in number. The inclusion of HBV and HDV patients would have been of benefit for improved adherence to HCV medications, but the management of these infections requires different approaches from HCV. Some contamination could have occurred during patients' clinic visits and sharing the same waiting area. Local validation of the translation could not be done, due to resource constraints.

This study highlights the valuable role of the pharmacist as part of a multidisciplinary team in the provision of individualized care for HCV patients. It emphasises the potential benefits of adopting a collaborative-care approach when managing HCV-infected patients at tertiary-care hospitals in Pakistan. Based on our findings, it is recommended that future research be directed toward exploring the role of a specialist pharmacist in the management of HCV-infected patients in secondary and primary health-care settings. The development of policies to

outline the role of specialist pharmacists is something that should be considered in Pakistan. The implementation of such roles, which include specialist pharmacy services and patient-centered care, in the context of LMICs is an emerging concept.<sup>46,47</sup> The management of chronic or communicable diseases, such as HCV, are potential areas where pharmacists can play a coordinated role in achieving optimum therapeutic outcomes.<sup>48</sup> Future qualitative research from LMICs would result in beneficial additions to the existing literature in developing clinical pharmacist roles in LMICs.

## Conclusion

This study shows that the provision of a specialist clinical pharmacy service focused for patient-centered care is an effective approach that would result in a positive impact on cure rates, HRQoL, and medication adherence in the HCV-infected population. Close monitoring of patients contributed to the achievement of positive outcomes in terms of goals of the therapy. This study suggests that clinical pharmacists be incorporated into multidisciplinary health-care team for care of HCV patients.

## Ethics Approval and Informed Consent

Ethical approvals was obtained from the Ethical Review Board of PIMS Hospital, Islamabad (F.1-1/2015/ERB/SZABMU), SIMS (IRB/2017/333/SIMS), and the Bioethics Committee of Quaid-i-Azam University, Islamabad (DFBS/2015-248). Written consent was obtained from all patients before the start of interview.

## Data Sharing

The appendix, statistical sheets, and data set will be available from the corresponding author at tofee.urrehman@qau.edu.pk.

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## Author Contributions

All authors contributed to data analysis and drafting and revising the article. MA, FR, and SA contributed substantially in acquisition of data. VP and TR made the initial concept and design. Interpretation of data was conducted by SA, SU, and SH. The initial draft of the manuscript was written by SA and TR. Finally, all authors approved the manuscript prior to submission and agreed to be accountable for all aspects of the work.

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## Disclosure

The authors declare that they have no financial or conflict of interest.

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